IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Application of Youlin Lin
Serial No. 338,382
Filed January 11, 1982 GROUP ART UNIT 126
For Chemical Compounds
Examiner B. Helfin

LETTER

TO THE COMMISSIONER OF PATENTS & TRADEMARKS
WASHINGTON, D.C. 20231

SIR:

This is in response to the Office Action of July 14, 1982.

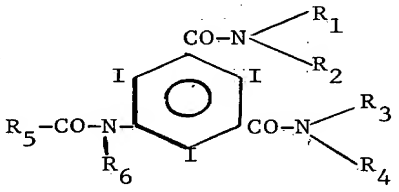
Reconsideration and allowance of this application are respectfully requested in view of the comments which follow.

Applicant's invention is directed to a novel compound N,N-bis-(2,3-dihydroxypropyl)-5-[N-(2-hydroxy-ethyl)-glycolamido]-2,4,6-triiodoisophthalamide, to radiological compositions containing such compound and to the use of such compositions for x-ray visualization. The novel compound of this invention is useful in various radiological procedures and has the outstanding property of high intercisternal toxicity. As will be shown it is truly unexpected that the compound of this invention would possess such a property.

Applicant respectfully traverses the rejection of all claims under 35 U.S.C. 102 as anticipated by or, in the

alternative, under 35 U.S.C. 103 as obvious over Speck (German 2909439) either alone or in view of Nordal et al. (U.S. 4,250,113).

Speck discloses compounds having the following formula:



in which the amide moieties $CO-NR_1R_2$ and $CO-N-R_3R_4$ differ from one another and a procedure for preparing such compounds.

The Examiner contends that Speck generically teaches the claimed compound at pages 2 and 3 of the specification and its use as an x-ray contrast agent. Applicant respectfully disagrees with this contention.

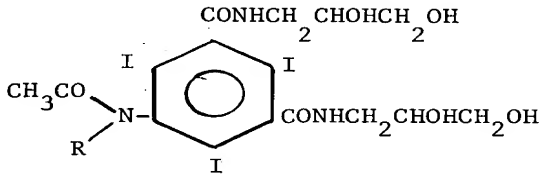
Speck discloses unsymmetrical compounds wherein the carbamyl groups in the 1 and 3 positions are different. Applicant's compound, on the other hand, is symmetrical wherein the carbamyl groups in the 1 and 3 positions are the same. Thus, Speck does not disclose compounds having symmetrical carbamyl groups useful as x-ray contrast agents. On page two of the unofficial translation, Speck discloses a procedure for the preparation of the compounds having different carbamyl groups in the 1 and 3 positions. This is a procedure for the preparation of unsymmetrical compounds as can be seen from the stepwise reaction with amines. This type of procedure would not normally be used to make symmetrical compounds. Thus, this procedure does not disclose a method for preparing compounds where the substituents on the two carbamyl groups are the same. Accordingly, Speck's disclosure does not anticipate

applicant's claimed compound and the rejection under 35 U.S.C. 102 should be withdrawn.

The Examiner contends that if the invention is not fully met by Speck at the minimum all the claims are deemed obvious in view of Speck. As mentioned, Speck discloses unsymmetrical non-ionic compounds where the carbamyl groups in the 1 and 3 positions are different. Speck states that this lack of symmetry overcomes disadvantages hereto seen with contrast media. The Examiner is directed to page 6 of the unofficial translation. Here, Speck says that the disadvantages could be entirely avoided or at least definitely decreased when the 1 and 3 position amide nitrogen atoms are differently substituted. Further advantages can be obtained if the substituents R_1 and R_2 are different from one another. Speck continues on page 7 with the advantages of his compounds, namely, stability, high iodine concentration, low osmatic pressure, low toxicity and alike. Speck attributes these improvements to the fact that his compounds are unsymmetrical wherein the two carbamyl groups are different. The compound of the instant invention, however, is a symmetrical non-ionic compound where the substituent on the two carbamyl groups are the same. Speck is not interested in symmetrical compounds for he says on page 6, that only a few derivatives on the basis of triiodoaminothalic acid amides have today proved sufficiently tolerable and chemically stable to be suitable as shadow producing rentagen contrast media for intravascular use. In these compounds, the 1 and 3 position amide groups are symmetrically substituted. That

is, both carboxyl groups are amidated with the same amine. Here, Speck teaches that symmetrical non-ionic compounds are likely not to be satisfactory x-ray contrast media. Clearly, he does not suggest modifying his compounds to make them symmetrical. In fact, he teaches away from making symmetrical compounds like the compound of Claim 1. Thus, the rejection of all the claims under 35 U.S.C. 103 over Speck alone is improper and should be withdrawn.

Recognizing the deficiencies of the Speck reference, the Examiner has attempted to supply them with Nordal et al. Nordal et al. disclose compounds having the following structure



where R represents the group $-CH_2CH_2OH$ or $-CH_2CHOHCH_2OH$. Their invention is directed to a "general x-ray contrast agent", i.e., an agent, according to them, that would be useful in all forms of intravascular visualization and myelography. Such an x-ray contrast agent should possess a package of favorable, essential parameters; namely, low toxicity, low osmology, low viscosity, high stability and the ability to produce solutions of high concentration but low ion concentration. Nordal et al. indicate that their invention is based upon the discovery that the indicated compounds which are not specifically disclosed in British 1,321,591 (U.S. 3,701,771) Almen et al. possesses, to at least the preferred levels indicated above, each of the above-mentioned properties and thus represent a substantial and valuable advance over the compounds generally disclosed in Almen et al. Additionally, they state that the compounds of their invention are easy to manufacture. One of the probable reasons for this is that they are symmetrical.

Thus, Nordal et al. specifically disclose only two compounds (generically disclosed in Almen et al.) which can be considered general x-ray contrast agents. Their compounds are symmetrical like applicant's in that they contain the same carbamyl groups in the 1 and 3 positions. In the 5 position they disclose only two substituents, namely, N-2,3-dihydroxypropyl acetamido and N-2-hydroxyethyl acetamido. They do not disclose applicant's claimed substituent in the 5 position. Clearly they do not suggest any other substituent, and surely not applicant's substituent because their specific substituents are responsible for their compounds being general x-ray contrast agents. It should be kept in mind that these two compounds among the many hundreds of compounds disclosed in the Almen et al. patent were found to be general x-ray contrast agents for both intravascular use and myelography. According to the patentees, this was a significant advance. Thus, Nordal et al. do not disclose or suggest another substituent in the 5 position of their compounds.

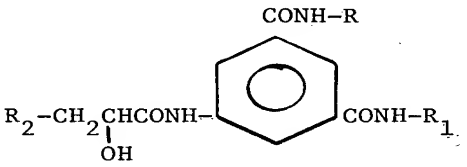
Likewise, Nordal et al. do not suggest modifying the Speck disclosure to give applicant's claimed compound for at least two reasons. (1) Nordal et al.'s compounds are symmetrical in the 1 and 3 positions. Clearly, this would not suggest modifying the unsymmetrical compounds of Speck to make them symmetrical when Speck says the reasons his compounds are good x-ray contrast agents is because they are unsymmetrical. (2) Nordal et al. disclose only two specific substituents in the 5 position. As mentioned, they do not suggest any other substituent in the 5 position. Thus, there is no suggestion to include a N-2-hydroxyethylhydroxy acetamido group in the 5 position of Speck's compounds and lose the benefit of Nordal et al.'s side chains. Furthermore, Speck does not specifically

disclose an example of a compound having a -N-2-hydroxyethylhydroxy acetamido group in the 5 position.

In summary, none of the references nor any combination thereof suggests applicant's compound. Accordingly, the rejection is improper and should be withdrawn.

Applicant respectfully traverses the rejection of all claims under 35 U.S.C. 103 over Nordal et al. (U.S. 4,250,113) in view of Felder et al. (I) (U.S. 4,001,323). Nordal et al. has been previously discussed. However, applicant wishes to reiterate that there is nothing in Nordal et al. that would suggest modifying their compounds in any manner and especially to modify them such that the 5 position would be the same as applicant's 5 position.

Recognizing this deficiency, the Examiner has attempted to supply it with Felder et al.(I). Felder et al. disclose compounds of the formula



where R and R_1 are 1-3-dihydroxyisopropyl or 2,3-dihydroxypropyl and R_2 is hydrogen or hydroxyl. Thus, instead of the 5 position being substituted by a mono or dihydroxypropionylamino group as in the above compounds, the compound of Claim 1 is substituted in the 5 position by a N-2-hydroxyethylhydroxy acetamido group. In this regard, it should be noted that the disclosure of Felder et al., (I) is very specific as to the substituent permitted in the

5 position. By reference to the working examples, i.e., it may be hydroxypropionylamino or dihydroxypropionylamino with the claims being limited to hydroxypropionylamino. Further, on this point, on lines 40-54 of Column 1, the patentee refers to Almen et al., U.S. 3,701,771, who disclose non-ionic x-ray contrast agents having "sugar" type substituents and state that such compounds are difficult to prepare and that mixtures of isomers produced as practically unable of being resolved to pure, individual compounds. It is further stated that the thermal stability of Almen et al. compounds is so low as to restrict their application. The patentees then assert that the compounds of U.S. 4,001,323 are free from the shortcomings of the chemically related known radiopaque compounds of Almen et al. Moreover, on lines 5-9 of Column 2 of U.S. 4,001,323, the patentees state that the advantages of their compounds over known compounds are thought to be due to the side chain, $R-CH_2-CHOH-CO-$ in the 5 position. Additionally, in the file history, it is stated that the claims are limited to compounds having in the 5 position a hydroxy-acylamino group having an available hydrogen on the nitrogen atom (page 4 of 6/21/76 amendment). Furthermore, this reference teaches that optically active substituents may provide improved water solubility and biological safety so that useful compounds may be obtained (see Column 4, line 47, et seq). Felder et al (I) specifically state that the compounds of the invention which "are optically active and particularly the L-enantimorphs which are prepared from derivatives of L-lactic acid are preferred". They are more soluble than the corresponding racemic compounds. Of the compounds disclosed in the Felder et al. (I) patent, only the L-lactimido is a clinically useful x-ray contrast agent.

(See Table I, Compound A.)

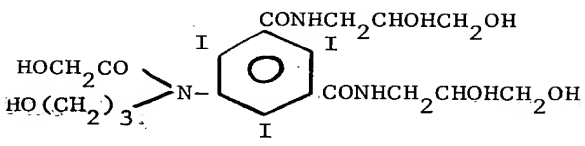
Under these circumstances, it is respectfully submitted that Felder et al. reference (I) not only fails to suggest the substitution of an N-(2-hydroxyethyl)-glycolamido group for the hydroxypropionyl group in the 5 position of Felder et al. (I) compounds, but in fact teaches away from any substituent in the 5 position. In fact, in the Felder and Pitre (the inventors) paper attached to the declaration of Dr. Hoey, compounds are disclosed having hydroxy acetamido groups in the 5 position which are nearly insoluble and not useful as an x-ray contrast agent (Table 2, P. S303, Compounds 1-3). Thus, those skilled in the art would predict, as Dr. Hoey says in his declaration, that hydroxy acetamido derivatives of amino-triiodoisophthalamide would not be chemically useful as x-ray contrast agents. Given the patentees own statements, one skilled in the art would be more likely to experiment with different substituents in the 1 and 3 positions so as not to lose the advantages attributed to this specific substituent in the 5 position by the patentees. Furthermore, since both the primary reference and the secondary reference relate to specific compounds having specific substituents in the 5 position, there is no reason to combine the teachings of the references. Furthermore, to modify the compounds of Nordal et al. in the 5 position with the side chain of Felder et al. (I) is contrary to the teaching of both of these references. Both Felder et al. (I) and Nordal et al. say the advantages of their compounds are due to the particular side chain in the 5 position. Clearly, Felder et al. (I) would not suggest replacing the N-hydroxyalkylacetamido of Nordal et al. with a N-hydroxyalkylhydroxyacetamido for at least two reasons.

First, Felder et al. (I) disclose that hydroxy acetamido substituents are essentially insoluble and second, Felder et al. (I) desire a nitrogen having an available hydrogen.

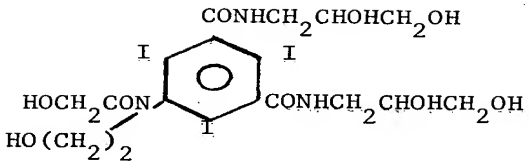
Applicant wishes to emphasize the high degree of unpredictability which exists in the field of non-ionic x-ray contrast media chemistry which renders it extremely difficult for those skilled in the art to predict the physical and pharmacological properties on the basis of structural features. In support of this position, applicant submits herewith the declarations of Dr. Brooke Hoey and Dr. Ronald M. Hopkins. Dr. Hoey's declaration expresses his opinion, as an experienced research chemist in the x-ray contrast media field, that it is not possible to predict with any degree of certainty the water solubility of candidate non-ionic x-ray contrast media. Dr. Hoey in his declaration illustrates this point by referring to the Pitre and Felder (the inventors on the secondary reference) article which is attached to his declaration. As can be seen in Table II of the article, compound 5, iopamidol, has a solubility of 90g per 100ml at 25°C. The closely analogous unsymmetric isomeric analog, compound 11, displays a solubility of 12g per 100ml in water at 25°C. Likewise, compound 6, symmetrical but isomeric with iopamidol shows a water solubility of 13g per 100ml. According to Dr. Hoey, compound 6 (compound C in the patent) would not be diagnostically useful as an x-ray contrast agent.

Dr. Hoey, in his declaration, compares the water solubility of a close analog, MP-420, to the compound of the present invention, MP-328. MP-420 and MP-328 have the

following structures:



MP-420



MP 420 differs from the compound of the present invention by a methyl group. According to Dr. Hoey, it could be predicted that this compound would have the same solubility as MP-328. In actual fact, its water solubility is less than 25% w/v (solubility of MP-328 is in excess of 100% w/v). According to Dr. Hoey, this once again illustrates the inability to predict water solubility on the basis of structure.

Dr. Hoey concludes that based upon his experience as an organic chemist with non-ionic x-ray contrast media, that there are few generalizations which apply to the design of such media and that it is difficult to synthesize compounds which are highly water soluble. Furthermore, it is impossible to predict whether a given compound will be water soluble prior to the synthesis and testing of the compound.

Dr. Hopkins' declaration sets forth his background as an experienced pharmacologist and gives the results of pharmacological testing carried out on a number of non-ionic x-ray contrast agents, including iopamidol, Felder et al. (I), C-29, Nordal et al., iohexol, Nordal et al., MP-301, Felder et al. (II), iopromide, Speck and MP-328 the compound defined in Claim 1. On the basis of animal testing of these compounds, Dr. Hopkins states that in his opinion these studies show that MP-328 is a

non-ionic contrast medium with CNS toxicity superior to the compounds tested and that such safety would be expected to be predictable in humans. The reason for this difference is not clear to Dr. Hopkins, but he concludes that it could not be predicted based on chemical structure relationships.

It is submitted that these declarations are entitled to great weight and consideration on the issue of obviousness and that when the structure and properties of the compound of Claim 1 are carefully considered in light of the prior art, as they must be, the subject matter of Claims 1 to 3 is clearly non-obvious within the meaning of 35 U.S.C. 103.

The Examiner states that the referenced compounds are directed to the same utility and the claimed compound has no more than the expected utility and would therefore be deemed obvious. However, the Examiner does not point out the alleged close relationship much less the basis for obviousness. In view of the dramatic and surprising properties exhibited by the compound of Claim 1, it is submitted under the PAPESCH Doctrine that applicant has overcome any obviousness rejection and that the Claims 1 to 3 are clearly patentable over the combination of references. Accordingly, the rejection is improper and should be withdrawn.

An early and favorable allowance is earnestly solicited.

Respectfully submitted,

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